

## **REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

### **I. Status of the Claims**

Claim 1 has been amended with support in the original specification, for example, at page 16, paragraph [0043]; and at page 45, paragraph [0135]. Claims 14, 39, 61, 77 and 96 have been amended to set forth the subject matter more clearly. Claim 41 has been amended to incorporate the recitations of claim 42 and claim 42 is cancelled accordingly. Claims 16, 63 and 79 have been amended to replace the trademarks with the corresponding generic terms.

Because no new matter is introduced, Applicants respectfully request entry of this amendment. Upon entry, claims 1-41 and 43-108 will be pending, with claims 8, 15, 16, 23-27, and 48-108 withdrawn.

### **II. Rejection of Claims under 35 U.S.C. § 112, second paragraph**

Claims 14, 39-40 and 42-43 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse the rejection.

Specifically, the Examiner contends that the terms “derivatives,” “significantly different,” and “bioequivalency” in claims 14, 39 and 42 are not defined. Without acquiescing to the stated basis for the rejection, the phrases “derivatives” and “significantly different” have been deleted. Moreover, claim 41 has been amended to specify the conditions of bioequivalency. Accordingly, the rejection should be withdrawn.

### **III. Provisional Double-Patenting Rejection**

Claims 1, 4-7, 9-12, 14, 18-21 and 28-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-15, 17-20, and 22-41 of copending Application No. 10/683,154. Applicants respectfully traverse the rejection.

Because the nonstatutory obviousness-type double patenting rejection is provisional at this time, Applicants choose to defer any action until the Examiner indicates that either application is allowed otherwise.

### **IV. Rejection of Claims under 35 U.S.C. § 102(b)**

Claims 1-5, 7 and 9-13 are rejected under 35 U.S.C. § 102(b) for alleged anticipation by Krause et al., International Journal of Pharmaceutics, 27: 145-155, 1985. Applicants respectfully traverse the rejection.

The present invention relates to a composition comprising at least one triamcinolone particles that have an effective average particle size of *less than about 2000 nm* and that have a phase selected from the group consisting of crystalline, amorphous and semi-crystalline, as well as at least one surface stabilizer adsorbed on the surface of the particles.

By contrast, Krause discloses nanoparticles of polylactic acid (PLA) loaded with triamcinolone acetonide. There is no mentioning whatsoever in the Krause publication that the size of the active ingredient, triamcinolone particles, is less than about 2000 nm and that the phase of the triamcinolone particles is crystalline, amorphous or semi-crystalline, as recited in claim 1. Rather, Krause teaches that nanoparticulated PLA particles form a “highly porous structure,” which is used as a matrix or carrier to deliver the triamcinolone acetonide. *See*, for example, page 146, second full paragraph; page 147, second paragraph; page 150, table 1, and page 152, first line below figure 5. Krause postulates that the consistent release pattern for all

batches and the quite rapid drug release was thought to be caused by the drug which is located on the surface of the PLA nanoparticles. *See pages 150-151.*

Moreover, as disclosed in the Introduction, the Krause publication relates to “the preparation and characterization of PLA nanoparticles as a drug carrier prepared by a modification of the procedure of Beck” (page 146, lines 17-20). Beck is German Patent No. 2940146, which corresponds to U.S. Patent No. 4,756,907. A copy of the U.S. patent is submitted herewith as Exhibit A. As shown in the figures of the ‘907 patent, the matrix materials, such as polylactic acid particles, form a cross-linked structure, onto which drugs or antibodies and antigens can be loaded. The process by which the particles in the ‘907 patent are formed are described at col. 5, lns. 27-37. Each of these techniques results in a micron-sized particle. *See Col. 6.* Nowhere in the ‘907 patent do the Applicants find a teaching to make particles less than 2000nm, let alone triamcinolone particles less than 2000nm without additional carrier materials or matrices.

Therefore, Krause does not teach or fairly suggest the claimed composition comprising at least one triamcinolone particle that have an effective average particle size of less than about 2000 nm and that have a phase selected from the group consisting of crystalline, amorphous and semi-crystalline with a surface stabilizer adsorbed on the surface of the particle. Accordingly, withdrawal of the anticipation rejection is warranted.

#### **V. Rejection of Claims under 35 U.S.C. § 103(a)**

Claims 6, 14, 17-22 and 28-47 are rejected under 35 U.S.C. § 103(a) for alleged obviousness over U.S. Patent No. 5,049,389 and U.S. Patent No. 5,043,165, both to Radhakrishnan, in view of U.S. Patent No. 5,744,155 to Friedman. Applicants respectfully traverse the rejection.

At the outset, Applicants note that the Examiner did not include any independent claim in the obviousness rejection set forth in this section. Pursuant to MPEP 2143.03, any claims

dependent from a nonobvious independent claim are also nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

The claims under the obviousness rejection are all dependent directly or indirectly from claim 1, which is not included in the rejection, implying that claim 1 is nonobvious over the cited art. For this reason alone, the claims in question are also nonobvious.

Nonetheless, the Applicants address the rejection of the dependent claims. Although the rejection cites to both U.S. Patent Nos. 5,049,389 and 5,043,165, the rejection discusses in detail the '389 patent and merely mentions the '165 patent as teaching a topical dosage form. Applicants comments are limited to the '389 patent for brevity of this response.

The Examiner alleges that the '389 patent teaches triamcinolone particles of the claimed size and points to column 14, lines 47-48 and 64-65 for support. The Examiner also acknowledges that "Radhakrishnan does not teach the bioadhesive property and/or characteristics of said invention" but cites to Friedman as teaching those elements. The Examiner did not specify which Radhakrishnan patent lacks the teaching of these elements, and Applicants cannot find these elements in both Radhakrishnan patents. Therefore, the Applicants assume that these elements are not taught in both the Radhakrishnan patents (i.e., the '389 and the '165 patents).

Notwithstanding the above, Applicants respectfully disagree that column 14, lines 47-48 and 64-65 of the '389 patent teaches triamcinolone particles of the claimed size. For the ease of reference, the relevant content of the '389 patent is reproduced below (emphasis added):

*"...steroids may be solubilized in surfactant micelles and nebulized into small aerosol particles...the mixture is filtered over filter with pore sizes smaller than steroid crystals, usually using 0.1-1 $\mu$  filter..."*

The last sentence at col. 14, lns 66-68 states:

*"Filter, on which the undissolved drug is deposited, is discarded and the micelle filtrate is used for nebulization as described below.*

Clearly, the '389 patent teaches removal of any undissolved drug from the micelles before they are nebulized. No crystallized drug particles remain in the micelles. One skilled in the art would thus not read the '389 patent as teaching a composition comprising, *inter alia*, triamcinolone particles that have an effective ***average particle size of less than about 2000 nm*** and that have a phase selected from the group consisting of ***crystalline, amorphous and semi-crystalline***, as recited in claim 1.

The Examiner further relies on Friedman for the alleged teachings of "bioadhesive property" and combination of additional "non-steroidal drugs." The limitations of the '389 and the '165 patent are discussed above, i.e., they do not teach a composition comprising triamcinolone particles that have an effective ***average particle size of less than about 2000 nm*** and that have a phase selected from the group consisting of ***crystalline, amorphous and semi-crystalline***. Although the Examiner cites to Friedman for a different teaching, Applicants point out that Friedman does not cure the deficient teachings of the Radhakrishnan patent. For at least this reason, the Radhakrishnan patents alone or in combination with Friedman fails to teach or suggest the claimed invention. Therefore, withdrawal of the rejection is respectfully requested.

#### CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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